Assessment of prostate cancer with integrated CT-perfusion using a sector-wise approach

Ferrari, Matteo ; Huellner, Martin ; Pauli, Chantal ; Seifert, Burkhardt ; Danuser, Hansjörg ; Veit-Haibach, Patrick ; Mattei, Agostino

Abstract: OBJECTIVE: The role of computed tomography perfusion (CTP) in characterizing primary prostate cancer (PCa) is not definitely known. The aim of the present study was to investigate the relationship between CTP parameters and histopathological features of PCa tissue, using a sector-wise approach. MATERIAL AND METHODS: Fifty-one patients with biopsy-proven PCa underwent prospectively a CTP scan prior to radical prostatectomy. Blood flow (BF), mean blood volume (BV) and mean transit time (MTT) were calculated, with the prostate being divided into eight sectors. Corresponding sector-wise histopathological analysis of whole-mount prostatectomy specimens was performed to determine tumoral area (mm(2)), mean microvessel density (MVD), Gleason patterns (primary, secondary) and total Gleason score. Spearman's rank correlation coefficient was used to analyze the association between CTP and histopathological parameters. RESULTS: BF correlated weakly with tumoral area [s coefficient (p-value): 0.25 (0.00)] and MVD [s coefficient (p-value): 0.23 (0.00)]. No valuable correlation was found between CTP parameters and primary and secondary Gleason patterns, whereas total Gleason score was weakly correlated with BV [s coefficient (p-value): 0.22 (0.00)] and MTT [s coefficient (p-value): 0.25 (0.00)]. CONCLUSION: BF correlates weakly with size and vascularity of PCa. There is a need for further studies to elucidate the association between CTP parameters and other histopathological parameters.

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UROONCOLOGY

Original Article

Assessment of prostate cancer with integrated CT–perfusion using a sector–wise approach

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ABSTRACT

Objective: The role of computed tomography perfusion (CTP) in characterizing primary prostate cancer (PCa) is not definitely known. The aim of the present study was to investigate the relationship between CTP parameters and histopathological features of PCa tissue, using a sector-wise approach.

Material and methods: Fifty-one patients with biopsy-proven PCa underwent prospectively a CTP scan prior to radical prostatectomy. Blood flow (BF), mean blood volume (BV) and mean transit time (MTT) were calculated, with the prostate being divided into eight sectors. Corresponding sector-wise histopathological analysis of whole-mount prostatectomy specimens was performed to determine tumoral area (mm^2), mean microvessel density (MVD), Gleason patterns (primary, secondary) and total Gleason score. Spearman's rank correlation coefficient was used to analyze the association between CTP and histopathological parameters.

Results: BF correlated weakly with tumoral area [ϱs coefficient (p-value): 0.25 (0.00)] and MVD [ϱs coefficient (p-value): 0.23 (0.00)]. No valuable correlation was found between CTP parameters and primary and secondary Gleason patterns, whereas total Gleason score was weakly correlated with BV [ϱs coefficient (p-value): 0.22 (0.00)] and MTT [ϱs coefficient (p-value): 0.25 (0.00)].

Conclusion: BF correlates weakly with size and vascularity of PCa. There is a need for further studies to elucidate the association between CTP parameters and other histopathological parameters.

Keywords: Computed tomography; Gleason score; multimodal imaging; perfusion imaging; prostate cancer.

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Introduction

The technique of computed tomography perfusion (CTP) imaging in oncology is based on the effects of tumoral angiogenesis.[1] Tumor vessels increase permeability and blood volume of the tissue, resulting in different patterns of contrast enhancement of viable tumor tissue in CT, as opposed to healthy tissue.[2] The combination of such functional parameters with morphological imaging has shown benefits for noninvasive characterization of several tumor types, tumor staging and assessment of therapy response.[3,4]

Although evidence-based guidelines and prospective clinical trials are currently lacking, multiparametric magnetic resonance imaging (MRI), using a combination of high-resolution T2-weighted images and at least two functional MRI techniques, is today the recommended technique for the noninvasive diagnosis and local staging of prostate cancer (PCa).[5] Given the increasing availability of MRI, CTP may represent a diagnostic chance for a minority of patients with contraindications to MRI, such as cases with implanted cardiac devices, or institutions not equipped with MR scanners.

The role of CTP in PCa is not well understood today, and only a few studies are currently available. CTP of the prostate had long time been hampered by technical difficulties which have been mostly overcome by recent advances in CT technique.[6] CTP analysis of the prostate is a robust technique, CTP parameters of the prostate are not influenced by tracer kinetics model used and colour-coded CTP maps reduce the risk of inter-observer differences.[7,8] Unlike MR perfusion, which relies on a change of signal intensities, the concept of CTP is based on tissue density and thus allows for a direct quantification. However, CTP study results obtained in PCa patients are partially discrepant, probably owing to the zonal architecture of the prostate and frequent coexistence of several diseases, such as benign prostatic hyperplasia (BPH), fibrosis, and prostatitis, as well as the ambigious nature of PCa itself (multifocal, microfocal, diffusely infiltrating etc.). A comparison between *in vivo* CTP parameters and histopathological markers of PCa angiogenesis has been performed only in a limited number of studies.[9,10]

Recently, CTP using an *en-bloc* approach has demonstrated that perfusion parameters may predict the aggressiveness of PCa more precisely than histopathological findings of biopsy specimens.[11] However, any correlation between perfusion parameters and Gleason score could not be demonstrated, which is usually present between Gleason score, and MRI perfusion findings.[12,13] The aim of our study was to investigate the relationship between CTP parameters and histopathological features of PCa tissue using a comprehensive, sector-wise approach.

Material and methods

Patient population

A cohort of ninety-eight consecutive male patients (median age 67 years, range 49 to 84) underwent a CTP scan. This prospective study was approved by the institutional review board and performed in accordance with the ethical standards laid down in the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria were: biopsy-proven PCa within the last 8 months, referral for initial staging examination by abdominal CT and/or bone scan, willingness to undergo an additional CT scan in order to acquire CTP image datasets, and scheduled start of therapy in less than 6 months. All patients were comprehensively assessed with a thorough medical history, and complete clinical and demographic data were collected, including serum concentrations of prostate-specific antigen (PSA). Exclusion criteria were: renal insufficiency (defined as renal clearance <30 mL/min); allergy or hypersensitivity to iodinated contrast medium, and untreated hyperthyroidism.

Fifteen patients were excluded after the scan for various reasons such as power injector malfunction (n=7), movement artifacts (n=1), beam hardening artifacts due to hip prosthesis (n=5), metal markers within the prostate (n=2), and presence of disseminated bone metastases (n=3). The remaining eighty patients with localized PCa subsequently underwent radical prostatectomy (RP). While 29 patients were subsequently excluded from the study because they did notundergo RP within the defined period of 150 days. Whole-mount histopathological analysis was performed in all prostatectomy specimens of the 51 evaluable patients.

Integrated CT-perfusion protocol

All CT scan were performed with a Somatom Definition Flash® scanner (Siemens Healthcare, Erlangen, Germany). The covered scan length was 7 cm. The scanning time was 60 s, rotation time 1 s; tube current 100 mAs and tube voltage 100 kV(p). Slice width was 5 mm with reconstruction increment of 3 mm. CT-perfusion scanning started with a delay of 10 s after the injection of 40 mL of iodinated contrast medium (Iopromidum 769 mg/mL, Ultravist® 370, Bayer Healthcare, Leverkusen, Germany) at an infusion rate of 4.5 mL/s.

If the patient had been referred for a staging CT, a CT scan of the abdomen was acquired subsequently after injection of another 60 ml of contrast medium and after a delay of 40 s (tube voltage 120 kV(p), quality reference tube current 210 mAs, pixel matrix 512x512, reconstructed slice thickness 2 mm, increment 1.5 mm).

Two radiologists (M.H., P.V.H.) performed all image analysis in consensus. Perfusion parameters blood flow (BF), blood volume (BV) and mean transit time (MTT) were determined using a commercially available computer workstation with dedicated perfusion evaluation software (Syngo Volume Perfusion CT Neuro, Siemens, Forchheim, Germany). The processing thresholds were 0 HU and 150 HU. The window width and center for reference vessel input were set to 300 HU and 150 HU, respectively. BF, BV and MTT color-coded maps were generated with a sequential two-compartment model (Figure 1). BF is defined as the amount of blood flowing through 100 mL of prostate tissue within one minute, MTT as the average time of contrast agent residence within the prostate tissue, and BV as the amount of blood within 100 mL of prostate tissue. For every patient, an individual arterial input fraction was determined by placing an analytic region of interest (ROI) into the external iliac artery to achieve a time attenuation curve (TAC), assuming that the TACs derived from internal and external iliac arteries were similar.

Data acquisition was performed, dividing the prostate volume on CT into eight sectors (right/left, anterior/posterior, superior/inferior).

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Histopathological analysis

One expert pathologist (C.P.) performed all histopathological analyses. After fixation, the entire prostate was cut into horizontal slices. Every slice was divided into eight sectors using a standardized approach in order to achieve sections corresponding to the sectors on CT as mentioned above. Specimens were cut in 4 μm sections. For each of the eight sectors, the tumoral area (mm^2), distance (mm) to the surgical resection margins and Gleason score were determined after hematoxylin-eosin staining. The mean intra-tumoral microvessel density (MVD; vessels per mm^2) was assessed quantitatively after immunohistochemical CD34 staining [Bond™ ready-to-use primary antibody CD34 (QBEnd/10)] and scanning with a Ventana™ slide scanner (Ventana iScan, Ventana Medical System, Roche). At least three photographs per section were used for visual counting using Image-J (public domain, Java-based image processing program developed at the National Institutes of Health, U.S.).

Main outcome measures

The primary end point of this study was to assess the association between CTP parameters (BF, BV, MTT) and histopathological parameters of PCa [tumoral area, primary and secondary Gleason pattern, total Gleason score, MVD] by using a sector-wise approach.

Statistical analyses

Categorical variables were presented as frequencies, quantitative data as mean (standard deviation, SD) or median with range. Spearman's rank correlation coefficient was used to analyze the correlation between sector-wise CTP values (BF, BV, MTT) and histopathological data [PCa area, primary and secondary Gleason pattern, total Gleason score, MVD]. Statistical analysis was conducted using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). All tests were two-sided, with level of significance set to 0.05.

Results

Table 1 lists patient demographic characteristics and descriptive statistics. Table 2 details the values of prostate CTP parameters and the histopathological data obtained from surgical specimen analysis.

Patient age showed a moderate correlation with MVD [ϱs coefficients (p-values): 0.31 (0.00)], but no significant correlation with tumoral area, primary (all ϱs coefficients <0.2), and secondary Gleason patterns. Conversely, PSA showed a moderate correlation with all analyzed histopathological variables [ϱs coefficients 0.38; 0.39; 0.31 and 0.32 for MVD, tumoral area, primary and secondary Gleason patterns, respectively, all p<0.01].

The relationship between CTP parameters and histopathological parameters is shown in Table 3. BF correlated weakly with the tumoral area [ϱs coefficient (p-value): 0.25 (0.00)] and with MVD [0.23 (0.00)]. BV and MTT were weakly correlated with total Gleason score [0.22 (0.00); 0.25 (0.00), respectively]. No valuable correlation was found between CTP parameters and primary and secondary Gleason patterns.

Discussion

Today, multiparametric MRI including perfusion is the recommended technique for the non-invasive assessment of PCa. However, some patients have contraindications to MRI, and not all institutions do have access to an MRI scanner. These are selected disease states where CTP imaging might play a clinical role. Besides, CTP imaging is performed much faster than MRI, its application is more convenient for the patient, and can easily be combined with an abdominal staging CT as part of the same

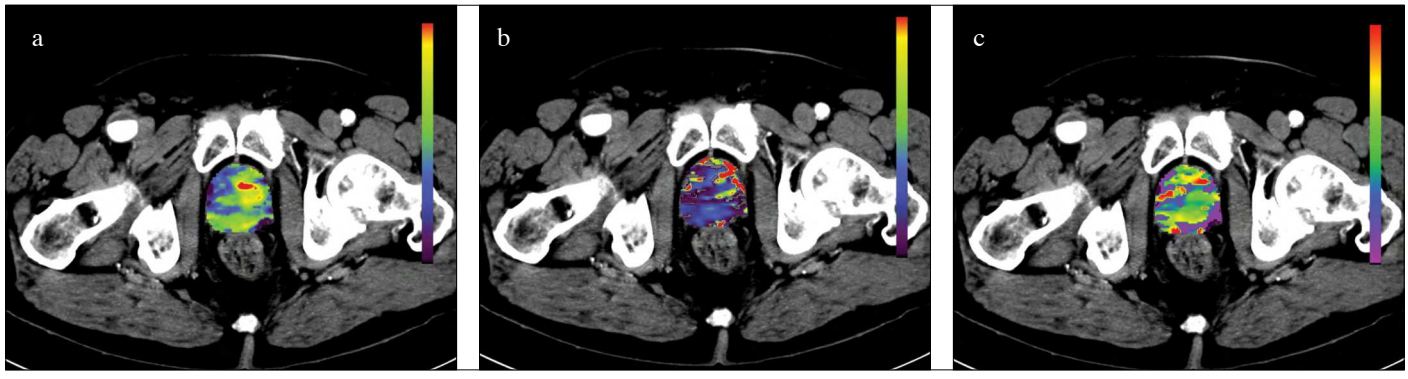

Figure 1. a-c. Computed tomography (CT)-perfusion imaging of one patient with prostate cancer, Gleason score 7 (3 + 4). (a) Colour-coded map of perfusion parameter blood flow (BF) (28.5 mL/100 mL min^{-1}; scale 0-40); (b) blood volume (BV) (4.1 mL/100 mL; scale 0-15) and (c) mean transit time (MTT) (8.1 seconds, scale 0-40)

examination, taking only 60 sec of extra time. CTP also allows for a direct quantification of parameters, unlike MRI. These characteristics render it a possible alternative for PCa patients, in cases where MRI cannot be performed.

Experimental work has also shown the usefulness of CTP for response assessment to radiotherapy and anti-angiogenic drugs.[14,15] One inherent drawback of CTP is the additional radiation burden delivered to the patient, requiring a well-considered weighing of potential benefits of cancer characterization. It should however be noted that the prostate-though being the most sensitive organ within the field - in any way will undergo organ-destructive treatment, be it by radiotherapy or by prostatectomy. In our study, the mean effective radiation dose to each individual was 25.6 mSv, which is within the range of current oncological perfusion studies.[16]

Table 1. Demographic and clinical data (n=51)

	Median	Range
Age (years)	65	49-73
Δt CT-RP (days)	62	10-145
	Mean (SD)	
PSA (ng/mL)	12 (15)	
	No.	**Frequency (%)**
Surgical approach		
RRP	9	18
RARP	42	82
Pathologic stage		
T2a	2	3.9
T2c	40	78.4
T3a	5	9.8
T3b	4	7.8

Δt CT-RP, time interval between computed tomography (CT) and radical prostatectomy (RP); PSA: prostate specific antigen; RRP: retropubic radical prostatectomy; RARP: robot-assisted radical prostatectomy; SD: standard deviation.

Table 2. Prostate parameters (n=408 sectors)

CT-perfusion	**Mean (SD)**	
BF (mL/100 mL x min^{-1})	39.5 (18.0)	
BV (mL/100 mL)	5.1 (2.9)	
MTT (s)	9.4 (7.1)	
Histopathology	**Median**	**Range**
PCa area (mm^2)	15.2	0.3-559.1
Primary Gleason pattern	3	3-4
Secondary Gleason pattern	3	3-5
	Mean (SD)	
MVD (n/mm^2)	148.9 (61.9)	

BF: blood flow; BV: blood volume; MTT: mean transit time; MVD: microvessel density; PCa: prostate cancer; SD: standard deviation.

Main methodological limitations of CTP of the prostate are related to poor anatomical intraprostatic detail, its inability both to detect small tumors, and also to assess extracapsular extension of the disease. A recent *en-bloc* approach has shown that patients with high-grade and intermediate-grade PCa can be more precisely differentiated with CTP rather than with biopsy.[11] However, a more comprehensive approach is desired that could potentially locate and characterize the tumor within the prostate. Thus we investigated CTP using a sector-wise approach.

Microvessel density serves as a marker of PCa-associated angiogenesis.[17,18] Studies have shown that MVD is higher in PCa than in benign prostate tissue.[19,20] Yeung et al.[21] investigated the relation between MVD and PCa *in vitro* perfusion analyzed with micro-CT. Vessels in malignant regions were tiny and did not have an apparent lumen. This suggests that - although MVD can be considered a marker of neoangiogenesis from a pathological point of view, however from a functional point of view MVD may not be linearly associated with perfusion, due to the potential presence of functionally non- patent vessels. The situation might be different under *in vivo* conditions. The *in vivo* use of CTP is based on the rationale that tumor angiogenesis is essential for cancer growth and CTP parameters are indirectly related to the micro-anatomical changes that characterize this process.[4]

Ives et al.[10] evaluated ten subjects with CTP using a 16-slice scanner before RP. Prostate specimens were divided into 6 sectors. A significant correlation between the area of maximum CT perfusion and PCa location was present only in the 2 subjects with the highest Gleason scores (8 and 10) and the highest tumor volume (≥50% in ≥1 sextant region). Besides the small

Table 3. Correlation coefficient of CT-perfusion and histopathologic parameters of prostate (n=408 sectors)

	BF ϱs (p)	**BV ϱs (p)**	**MTT ϱs (p)**
PCa area	0.25 (0.00)	0.16 (0.00)	0.03 (0.6)
Primary Gleason pattern	0.10 (0.09)	0.19 (0.00)	0.19 (0.00)
Secondary Gleason pattern	0.10 (0.11)	0.16 (0.07)	0.22 (0.06)
Total Gleason score	0.12 (0.05)	0.22 (0.00)	0.25 (0.00)
MVD	0.23 (0.00)	0.16 (0.00)	0.09 (0.14)

BF: blood flow; BV: blood volume; MTT: mean transit time; MVD: microvessel density; PCa: prostate cancer; ϱs: Spearman's rho correlation coefficients.

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number of patients, their study was limited mainly by a different CTP protocol, and technical factors due to their currently outdated scanner type, such as artifacts from pelvic bones, low temporal resolution, and limited axial coverage. Osimani et al.[9] performed CTP in twenty-two patients on a 64-slice scanner, with histolopathology as standard of reference. They reported a significant correlation between BV and MVD (coefficient 0.6), which was not observed in our study. Luczynska et al.[22] reported a weak positive correlation between CTP-derived BV and MVD (correlation coefficient 0.20) in 110 PCa patients using a 16-slice scanner. In our study we found a correlation of MVD only with BF, but not with BV. Differences might be due the sector-wise approach, which might weaken such a potential relationship.

Besides, the CD34 staining for MVD analysis might be inferior to CD31 staining, but it was used in ours as well as in the other studies mentioned above.[9,22] Notably, our findings for BV are similar to results of MRI studies where this perfusion parameter does not consistently correlate with MVD.[23,24] In line with Osimani et al.[9] we observed no correlation with MVD, while Luczynska et al.[22] reported a weak but positive correlation. The correlation we found between MVD and BF might reflect increased vascularity of PCa tissue. This is further supported by the fact that MVD correlated with the size of tumor area in our study, which is probably due to a linear growth of vessels with the dimensional development of tumors.[25]

We also investigated the association between CTP parameters and Gleason grading. Luczynska et al.[26] analyzed only the peripheral zone, with periurethral tissue and the hyperplastic transition zone being excluded. They found higher BF and BV in high-grade PCa (Gleason score >7) rather than in intermediate- (Gleason score=7) and low-grade (Gleason score <7) tumors. Similar results were found recently by Huellner et al.[11] using an *en-bloc* approach. In our study, in which we used a sector-wise approach, we have found correlation between Gleason score and BV but not with BF. BV is consistently reported to be associated with PCA grading and/or vascularity in different study populations and in CTP studies using different technical approaches (9, 11, 22, 26 and present study). These results raise the question for a potential role of BV for non-invasive PCa characterization via determining tumor aggressiveness.

One strength of our study is the use of a sector-wise approach. This method might be more appropriate than more complex methods that are potentially subject to the typically diffuse nature of PCa and to potential shortcomings of millimeter-wise comparisons. On the other hand, it might also be more appropriate to use than more coarse methods, which despite being fast processing and user-friendly, might not appreciate smaller lesions well enough.[9,11]

Our study has several limitations. First, the retrospective matching of CT slices and histopathologic sections is prone to misregistration to some extent. However, we tried to minimize this potential error by careful and consensual matching of the respective slices and sections. Besides, the usually diffuse nature of PCa likely foils any attempt of true coregistration. Second, we did not account for coexisting prostatic pathology, such as BPH, fibrosis and inflammation. However, this was not also the goal of our study, and no cut-off values of CTP parameters exist for the differentiation of these conditions. Third, the time interval between CTP scan and prostatectomy may have influenced the relationship of CTP parameters and histopathological parameters. However, PCa is known to be a slowly growing inert tumor, and thereby such bias is not very likely. Lastly, technical limitations and inter -reader variability may affect the reproducibility and validity of CTP analysis; however our study was conducted according to recent guidelines and our rather lengthy scanning protocol facilitates a high reproducibility.[2,27,28]

Our study is the first CTP study to analyze prostate cancer using a sector-wise approach. Blood flow correlates both with tumoral area and MVD, whereas blood volume correlates with the Gleason score. These results suggest that a sectoral analysis is suitable for the non-invasive characterization of PCa with CTP. There is still a need for further studies to better define potential clinical implications of this technique.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.M., H.D., P.V.H., M.H.; Design – M.H., C.P.; Supervision – A.M., P.V.H., H.D.; Resources – A.M., P.V.H., H.D.; Materials – A.M., P.V.H., H.D.; Data Collection and/or Processing – M.F., M.H., C.P.; Analysis and/or Interpretation – M.F., M.H., B.S.; Literature Search – M.F., M.H.; Writing Manuscript – M.F., M.H.; Critical Review – M.F., M.H., A.M., H.D.

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References

1. Goh V, Ng QS, Miles K. Computed tomography perfusion imaging for therapeutic assessment: has it come of age as a biomarker in oncology? Invest Radiol 2012;47:2-4. [CrossRef]

2. Miles KA, Lee TY, Goh V, Klotz E, Cuenod C, Bisdas S, et al. Current status and guidelines for the assessment of tumour vascular support with dynamic contrast-enhanced computed tomography. Eur Radiol 2012;22:1430-41. [CrossRef]
3. Miles KA. Perfusion CT for the assessment of tumour vascularity: which protocol? Br J Radiol 2003;76:36-42. [CrossRef]
4. Miles KA. Functional CT imaging in oncology. Eur Radiol 2003;13:134-8. [CrossRef]
5. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65:124-37. [CrossRef]
6. García-Figueiras R, Goh VJ, Padhani AR, Baleato-González S, Garrido M, León L, et al. CT perfusion in oncologic imaging: a useful tool? AJR Am J Roentgenol 2013;200:8-19. [CrossRef]
7. Korporaal JG, van Vulpen M, van den Berg CA, van der Heide UA. Tracer kinetic model selection for dynamic contrast-enhanced computed tomography imaging of prostate cancer. Invest Radiol 2012;47:41-8. [CrossRef]
8. Win Z, Ariff B, Harvey CJ, Rangi P, Eckersley R, Hawtin K, et al. Comparative study of experienced vs non-experienced radiologists in assessing parametric CT images of the response of the prostate gland to radiotherapy. Br J Radiol 2008;81:572-6. [CrossRef]
9. Osimani M, Bellini D, Di Cristofano C, Palleschi G, Petrozza V, Carbone A, et al. Perfusion MDCT of prostate cancer: correlation of perfusion CT parameters and immunohistochemical markers of angiogenesis. AJR Am J Roentgenol 2012;199:1042-8. [CrossRef]
10. Ives EP, Burke MA, Edmonds PR, Gomella LG, Halpern EJ. Quantitative computed tomography perfusion of prostate cancer: correlation with whole-mount pathology. Clin Prostate Cancer 2005;4:109-12. [CrossRef]
11. Huellner MW, Pauli C, Mattei A, Ross S, Diebold J, Vosbeck J, et al. Assessment of prostate cancer with dynamic contrast-enhanced computed tomography using an en bloc approach. Invest Radiol 2014;49:571-8. [CrossRef]
12. Li L, Margolis DJ, Deng M, Cai J, Yuan L, Feng Z, et al. Correlation of gleason scores with magnetic resonance diffusion tensor imaging in peripheral zone prostate cancer. J Magn Reson Imaging 2015;42:460-7. [CrossRef]
13. Hambrock T, Somford DM, Huisman HJ, van Oort IM, Witjes JA, Hulsbergen-van de Kaa CA, et al. Relationship between apparent diffusion coefficients at 3.0-T MR imaging and Gleason grade in peripheral zone prostate cancer. Radiology 2011;259:453-61. [CrossRef]
14. Harvey CJ, Blomley MJ, Dawson P, Morgan JA, Dooher A, Deponte J, et al. Functional CT imaging of the acute hyperemic response to radiation therapy of the prostate gland: early experience. J Comput Assist Tomogr 2001;25:43-9. [CrossRef]
15. Cyran CC, von Einem JC, Paprottka PM, Schwarz B, Ingrisch M, Dietrich O, et al. Dynamic contrast-enhanced computed tomography imaging biomarkers correlated with immunohistochemistry for monitoring the effects of sorafenib on experimental prostate carcinomas. Invest Radiol 2012;47:49-57. [CrossRef]
16. Goh V, Dattani M, Farwell J, Shekhdar J, Tam E, Patel S, et al. Radiation dose from volumetric helical perfusion CT of the thorax, abdomen or pelvis. Eur Radiol 2011;21:974-81. [CrossRef]
17. Kaygusuz G, Tulunay O, Baltaci S, Gogus O. Microvessel density and regulators of angiogenesis in malignant and nonmalignant prostate tissue. Int Urol Nephrol 2007;39:841-50. [CrossRef]
18. Huss WJ, Hanrahan CF, Barrios RJ, Simons JW, Greenberg NM. Angiogenesis and prostate cancer: identification of a molecular progression switch. Cancer Res 2001;61:2736-43.
19. Bono AV, Celato N, Cova V, Salvadore M, Chinetti S, Novario R. Microvessel density in prostate carcinoma. Prostate Cancer Prostatic Dis 2002;5:123-7. [CrossRef]
20. Erbersdobler A, Isbarn H, Dix K, Steiner I, Schlomm T, Mirlacher M, et al. Prognostic value of microvessel density in prostate cancer: a tissue microarray study. World J Urol 2010;28:687-92. [CrossRef]
21. Yeung AK, Atri M, Sugar L, Klotz L. Feasibility and safety of silicone rubber contrast-enhanced microcomputed tomography in evaluating the angioarchitecture of prostatectomy specimens. Transl Oncol 2011;4:173-7. [CrossRef]
22. Luczynska E, Blecharz P, Dyczek S, Stelmach A, Petralia G, Bellomi M, et al. Perfusion CT is a valuable diagnostic method for prostate cancer: a prospective study of 94 patients. Ecancermedicalscience 2014;8:476. [CrossRef]
23. Oto A, Yang C, Kayhan A, Tretiakova M, Antic T, Schmid-Tannwald C, et al. Diffusion-weighted and dynamic contrast-enhanced MRI of prostate cancer: correlation of quantitative MR parameters with Gleason score and tumor angiogenesis. AJR Am J Roentgenol 2011;197:1382-90. [CrossRef]
24. Franiel T, Lüdemann L, Rudolph B, Rehbein H, Stephan C, Taupitz M, et al. Prostate MR imaging: tissue characterization with pharmacokinetic volume and blood flow parameters and correlation with histologic parameters. Radiology 2009;252:101-8. [CrossRef]
25. Poon RT, Ng IO, Lau C, Yu WC, Yang ZF, Fan ST, et al. Tumor microvessel density as a predictor of recurrence after resection of hepatocellular carcinoma: a prospective study. J Clin Oncol 2002;20:1775-85. [CrossRef]
26. Luczynska E, Gasinska A, Blecharz P, Stelmach A, Jereczek-Fossa B, Reinfuss M. Value of perfusion CT parameters, microvessel density and VEGF expression in differentiation of benign and malignant prostate tumours. Pol J Pathol 2014;65:229-36. [CrossRef]
27. Ng CS, Chandler AG, Wei W, Anderson EF, Herron DH, Charnsangavej C, et al. Reproducibility of perfusion parameters obtained from perfusion CT in lung tumors. AJR Am J Roentgenol 2011;197:113-21. [CrossRef]
28. Ng CS, Chandler AG, Wei W, Anderson EF, Herron DH, Kurzrock R, et al. Effect of dual vascular input functions on CT perfusion parameter values and reproducibility in liver tumors and normal liver. J Comput Assist Tomogr 2012;36:388-93. [CrossRef]